

GENERAL CONSTRUCTION PATTERN OF HISTAMINE H₃-RECEPTOR ANTAGONISTS: CHANGE OF A PARADIGM

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Abstract: Novel ω -phenyl substituted and unsubstituted alkyl and alkenyl imidazole derivatives were prepared and tested for their antagonist activity *in vitro* and *in vivo* at histamine H₃-receptors. Some compounds showed high *in vitro* and *in vivo* H₃-receptor activity despite their structure bearing no polar moiety in the centre of the molecule which is a common structural feature of all other antagonists known. Quite probably there are further *in vivo* effects for some compounds resulting from other receptor interactions. © 1998 Elsevier Science Ltd. All rights reserved.

Since the discovery of the histamine H₃-receptor¹ a large number of different antagonists have been described.^{2,3} Due to their influence on H₃-auto- and H₃-heteroreceptors antagonists may prove to be potential drugs for the treatment of different diseases or conditions in the central nervous system like epilepsy,⁴ stress,⁵ memory and learning deficits⁶ as well as cognitive and sleep disorders.⁷ Although the antagonists described belong to different structural classes, they all have a general construction pattern in common² (Fig. 1).

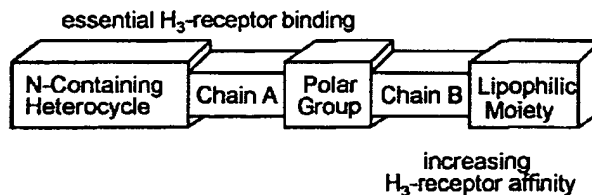


Figure 1. General construction pattern of histamine H₃-receptor antagonists

The *N*-containing heterocycle is an aromatic moiety which in most cases is an imidazole ring monosubstituted in 4-position. Almost all structural variations of this heterocycle led to a drastic loss in affinity. Chains A and B can be of different structure. The same is true for the polar group of which a large number of functionalities have been described by maintaining H₃-receptor affinity (for review see^{2,3}). Many *p*-halogen phenyls have been reported to be advantageous for the lipophilic moiety, but a lot of heterocycles or

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alkyl substituents were also tolerated by the receptor. Four different antagonists are shown in Figure 2 to demonstrate their community. Whereas the first three elements seemed to be essential for H₃-receptor affinity the last two elements seemed to increase affinity. The compounds described herein possess an alkyl or alkenyl moiety instead of the polar group. Thus this element is shown not to be essential for an interaction with histamine H₃-receptors.

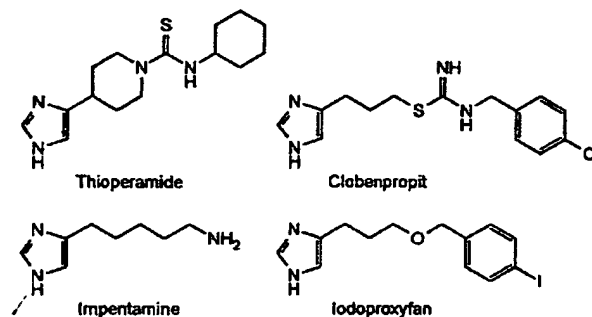
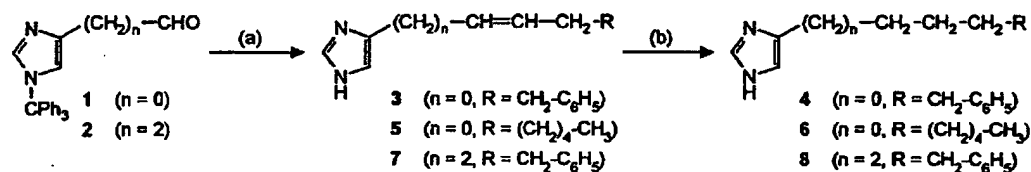


Figure 2. Structures of histamine H₃-receptor antagonists of different classes.

Chemistry.

The aldehydes as starting material are obtained by oxidation of the corresponding trityl protected alcohols. (1-Trityl-1*H*-imidazol-4-yl)methanol⁸ is conveniently oxidized into **1**⁹ with MnO₂, whereas Swern oxidation gave best results for the reaction with 3-(1-trityl-1*H*-imidazol-4-yl)propanol⁹ for the preparation of **2**¹⁰. Conventional Wittig reaction with **1** predominately resulted in the *Z*-configured alkene derivatives.¹¹ The configuration of **7** obtained by reaction with the propanal derivative **2** was not determined due to overlap of ¹H NMR signals of neighbouring methylene protons as well as that of alkenyl protons.¹² Acidolytic deprotection resulted in alkene derivatives in almost quantitative yields. Hydrogenation of the double bond was performed by heterogeneous catalysis under pressure (Scheme 1). All compounds were purified chromatographically, characterized in the form of their maleates (**3,4**) or oxalates (**5–8**), and gave satisfactory analytical results.

Scheme 1.



(a) i: [Ph₃P-CH₂-CH₂-R]Br, KOC(CH₃)₃, THF; 25–75%; ii: 6*N* HCl/acetone, reflux; 95%. (b) H₂ (10 bar), Pd/C (5%), MeOH; 95%.

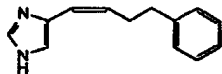
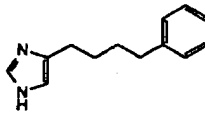
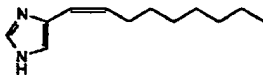
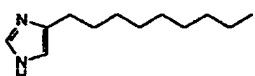
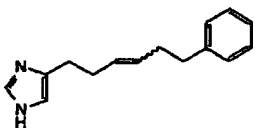
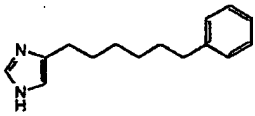
Pharmacology, Results, and Discussion.

Histamine H₃-Receptor *in Vitro* Assay on Synaptosomes of Rat Cerebral Cortex. The compounds were tested for their H₃-receptor antagonist activity in an assay with K⁺-evoked depolarization-induced release of [³H]histamine from synaptosomes of rat cerebral cortex according to Garbarg et al.¹³ (Table 1).

Histamine H₃-Receptor Antagonist *in Vivo* Potency in Mice. Increase in *N*-methylhistamine levels in Swiss mice brain 90 min after *p.o.* administration of the compounds was selected to screen histamine H₃-receptor antagonist *in vivo* activity¹³ (Table 1). The ED₅₀ values were calculated as mg free base • kg⁻¹.

Histamine H₁-, H₂-, and Muscarinic M₃-Receptor *in Vitro* Activity on Isolated Organs of Guinea Pig. Functional tests on guinea pig ileum for H₁- and M₃-receptors as well as on guinea pig atrium for H₂-receptor *in vitro* activity according to Ligneau et al.¹⁴ were used to investigate selectivity.

Table 1. Histamine H₃-Receptor *in Vitro* and *in Vivo* Activity of Compounds 3–8.

Compound	Structure	Antagonist H ₃ -receptor activity	
		<i>in vitro</i> K _i [nM] ($\bar{x} \pm s_{\bar{x}}$)	<i>In vivo p.o.</i> ED ₅₀ [mg kg ⁻¹] ($\bar{x} \pm s_{\bar{x}}$)
3		> 500	> 10
4		56 ± 13	2.2 ± 0.7
5		> 500	8.6 ± 1.2
6		~ 400	3.7 ± 0.9
7		42 ± 13	0.61 ± 0.06
8		88 ± 24	1.0 ± 0.3
Thioperamide ^a		4 ± 1	1.0 ± 0.5
Clobenpropit ^a		0.6 ± 0.1	26 ± 7

(a) Ref. ⁹

Histamine H₃-Receptor *in Vitro* Testing on Synaptosomes of Rat Cerebral Cortex. Compounds 3 and 5 possessing a (*Z*)-configured double bond in conjugation with the imidazole ring were devoid of any significant H₃-receptor affinity. Conjugation and electronic effects cannot be the reasons for this absence of interaction because very recently we have described a related (*E*)-configured derivative possessing moderate *in vitro* affinity.¹⁵ More likely, the alignment of the linker and the lipophilic group with compounds 3 and 5 is sterically not favourable. An improved receptor-ligand interaction can be concluded for the phenyl derivatives 4, 7, and 8. Whereas it may be possible to state for compound 7 that the double bond in the middle of the molecule mimics the polar group, it is clear that compounds 4 and 8 are devoid of such a structural element. Although compound 7 possessed slightly higher H₃-receptor potency, 4 and 8 were also H₃-receptor antagonists with remarkable affinity.

It might be speculated that the elements of the general construction pattern formerly thought to be essential were based on two essential interaction areas. By introducing another binding partner with the lipophilic moiety the resulting receptor-ligand interaction may be strong enough to omit the polar group maintaining affinity. Consequently it was shown that the polar group is not essential for antagonist H₃-receptor interaction, but by comparison of 7 and 8 this element increases affinity. By these data a three point-interaction model is suggested requiring two interaction points at least.

Histamine H₃-receptor *in Vivo* Testing in Mice Brain after *p.o.* Administration. The results for the phenyl compounds *in vivo* were in good agreement with their *in vitro* data. Although the *in vitro* potency for all compounds is more than one log-unit less than that for thioperamide, the novel highly lipophilic compounds might easily penetrate the blood-brain barrier presenting thus low ED₅₀-values. Whereas 8 was equipotent to the reference antagonist thioperamide, compound 7 was even more potent. (4-(6-Phenyl-3-hexen-1-yl)-1*H*-imidazole (7) is one of the compounds with the highest central *in vivo* potency reported. It serves as a novel lead for further optimization, which is currently under progress¹⁶.

The *in vivo* results for 5 and 6 are very astonishing. Although these compounds were almost inactive *in vitro* at H₃-receptors, they enhanced *in vivo* the concentration of *N*^ε-methylhistamine in brain. It cannot be excluded that the *in vivo* screening model can also detect additional effects able to apparently enhance the turnover of histamine, as shown by an increased concentration of its main metabolite in the assay. So far, H₃-receptor blockade appears as the sole pharmacological approach to enhance brain histamine turnover^{17,18}, but additional studies are required to clarify the mode of action of these compounds *in vivo*.

Compounds 3 and 4 were also tested *in vitro* at H₁-, H₂- and M₃-receptors to investigate if any of these related systems may be responsible for unpredictable *in vivo* activity. The activity found was below 5.5 (pD₂'-value) showing in each case that none of these receptors had influenced the H₃-receptor *in vivo* activity measured.

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11. ¹H NMR data (300 MHz, DMSO-D₆): 3-C₄H₄O₄ 8.91 (s, 1H, imidazole-2-H), 7.59 (s, 1H, imidazole-5-H), 7.24 (m, 5H, 5phenyl-H), 6.26 (d, *J*_{ax} = 12 Hz, 1H, imidazole-CH), 6.13 (s, 2H, maleic acid), 5.90 (m, 1H, imidazole-CH=CH), 2.77 (t, *J* = 7.4 Hz, 2H, phenyl-CH₂), 2.59 (m, 2H, phenyl-CH₂-CH₂); 5-C₂H₂O₄ 8.31 (s, 1H, imidazole-2-H), 7.33 (s, 1H, imidazole-5-H), 6.24 (d, *J*_{ax} = 11.5 Hz, 1H, imidazole-CH), 5.68 (m, 1H, imidazole-CH=CH), 2.31 (m, 2H, =CH-CH₂), 1.41–1.25 (m, 10H, 5CH₂), 0.84 (m, 3H, CH₃).
12. ¹H NMR data (300 MHz, DMSO-D₆): 7-C₂H₂O₄ 8.40 (s, 1H, imidazole-2-H), 7.29–7.14 (m, 6H, imidazole-5-H, 5phenyl-H), 5.36 (m, 2H, CH=CH), 2.57–2.23 (m, under solvent, 8H, 4CH₂).
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